REMARKS

Claims

Claims 1–29 are canceled without prejudice or disclaimer. Claims 30–40 are added by this paper.

Claim Amendments

New claims 30–40 are supported by the disclosure contained in, for example, the paragraphs bridging pages 14 and 15 of the specification, as originally filed.

It is respectfully submitted that the claim amendments do not raise new matter.

Specification

The specification has been amended as per the Examiner's suggestion. Withdrawal of the objection is courteously requested.

Rejection under 35 U.S.C. §102(b) over Modjtahedi

Claims 1–5 stand rejected under §102(b) as allegedly anticipated by Modjtahedi et al. (*Cellular Biophysics*, 1993). Applicants respectfully traverse the rejection.

Modjtahedi discloses ICR62 and ICR64 antibody species which bind to epitope C and epitope D on the external domain of EGFR, but fails to teach or suggest the claimed activity of the antibody molecules (for example, with respect to receptor binding and/or cell growth inhibition).

Thus, the reference does not describe, for example, a first and second antibody molecule against ErbB1 receptor which cause an enhanced ErbB1 blocking and/or inhibition and induction of down-regulation of ErbB1 receptor-specific pathway signaling as compared with a composition comprising said first or second antibody molecule. The cited reference fails to disclose the claimed activity of the antibody molecules.

More specifically, at page 142, Modjtahedi expressly states that two antibody molecules, for example, ICR61 and ICR62 antibody molecules, did not elicit enhanced growth inhibitory properties:

> What was more surprising was the results of the animal studies where again the effects observed were intermediate between those obtained for the individual antibodies. We had expected that the additional loading of antibody/cell that could be achieved by targeting two distinct epitopes on the EGFR would have led

> to enhanced tumor regression but this did not appear to be the case. Also, when both antibodies were of the IgG2b isotype (ICR61 and ICR62), we anticipated that they would act *synergistically* to give an enhanced response because of the possible additional activation of host effector mechanisms. Clearly, this was not the case. (Emphasis added)

Modjtahedi does not teach or disclose all the structural and/or functional elements recited in Applicants' claims. As such, the cited reference fails to anticipate Applicants' instant invention. Withdrawal of the rejection is respectfully requested.

Moreover, Modjtahedi does not render obvious the claims of the instant application insofar as there would be no motivation for a skilled artisan to devise and/or utilize a composition comprising the antibody molecules in a manner recited in Applicants' claims. As pointed out in the preceding paragraphs, the cited reference specifically states that a composition comprising the two antibodies directed against two distinct EGFR epitopes does not offer enhanced anti-tumor effects. As such, the compositions of the instant invention are also unobvious over the teachings of the cited reference.

Rejections under 35 U.S.C. §102(b)/§103(a) over Greene et al. (US 5,705,157)

The Office Action further alleges that the instantly claimed subject matter is anticipated, or in the alternate, rendered obvious by Greene et al. This contention is respectfully traversed.

Greene discloses antibodies against epidermal growth factor receptor and p185neu, p185c-neu or a homolog of p185neu. The reference further teaches that such monoclonal antibodies are useful in the targeting of tumors which express both epidermal growth factor receptors (ErbB1) and p185 neu, p185 c-neu or homologue of p185 neu or p185c-neu on the cell surfaces. ErbB2 is described as being a homolog of p185 neu or p185 c-neu. See, ABSTRACT and DETAILED DESCRIPTION sections of the cited reference.

Applicants submit that Greene's composition comprising anti-ErbB1 and anti-ErbB2 antibodies are distinct from the molecules claimed herein. Most of Greene's disclosure is directed to ErbB2 receptor molecules. For example, see, col. 3, lines 1–55 and the disclosure contained in the paragraphs spanning cols. 10–12 (Examples section) of Greene et al. In the experimental portion of the disclosure, cellular and

biochemical effects of p185 neu, p185 c-neu-mediated signal transduction are described. Antibody molecules which are directed against the p185 neu cell-surface proteins are utilized. Greene is silent with respect to compositions comprising antibodies directed against different epitopes located on an ErbB1 receptor molecule, wherein said epitopes are located on the ligand-binding domain of the ErbB1 receptor molecule.

Since not all elements of Applicants' claims are taught or disclosed in the cited reference, Greene cannot anticipate. For anticipation, each and every element of Applicants' claims must be taught, either explicitly or implicitly, by the cited reference. Such has not been achieved here, and as such, the rejection must be withdrawn.

Greene in combination with Mendelsohn (US 4,943,533)

The Office Action at page 11 alleges that "it would have been prima facie obvious to combine the ErbB1 monoclonal antibody 425 or chimeric antibody (as taught by Greene) with the murine monoclonal antibody such as MAb225 (as taught by Mendelsohn)." Applicants respectfully traverse this contention.

A combination of the cited references would never lead to a skilled worker to the subject matter of the instant invention since neither Greene nor Mendelsohn teaches a composition comprising antibody molecules directed against the same ErbB1 receptor type. The cited references do not impart any teaching or suggestion that the claimed molecules impart enhanced activity. Compare, Applicants' claim 1. In view of what was known in the art (for example, see, Modjtahedi's disclosure, discussed *supra*), one of ordinary skill in the art would not have been motivated to combine the molecules. Even if one were to combine the teachings of all the references, there would be no way, absent hindsight, to arrive at the claimed structures because the primary reference is directed to molecules which are structurally distinct from the molecules of the instant invention. For example, the bulk of the disclosure in Greene is directed to inhibition of ErbB2 receptor molecule.

In view of the fact that Greene's disclosure is primarily drawn to ErbB2 receptor molecules, which are distinct from the targets of the instant invention, a skilled worker relying on a combination of the cited references would be directed away from the subject matter of the instant claims. Even at their broadest interpretation, a combination of Greene and Mendelsohn would fail to render obvious the instantly

claimed composition because Greene's antibodies are directed to two different receptor molecules. It is respectfully submitted that the Office Action has failed to meet the basic criteria for *prima facie* case of obviousness, and as such, the rejection under 35 U.S.C. §103(a) must be withdrawn.

To further support its contention, the Office Action recites *In re Kerkhoven* 205 USPQ 1069(CCPA 1980) to contend that it would be obvious to combine two molecules, each of which is allegedly taught by the cited teachings as being useful for the same purpose, to formulate a third composition, which is to be used for that same exact purpose. Applicants respectfully disagree with this analysis and submit that the recitation of *In re Kerkhoven* in this particular case is inappropriate.

It is respectfully submitted that the decision in Kerkhoven was made with respect to spray-dried detergent compositions comprising anionic and nonionic detergent materials, whereas the compositions of the instant invention comprise agents that are known in the art to have different biological targets and, as such, effects. The Examiner's expressed reliance on *In re Kerkhoven* is misplaced, especially in view of the disclosure contained in the specification. For example, in the Kerkhoven case, "it was determined that the claims require no more than mixing of the two conventional detergent compositions" and that "the appellant had not demonstrated any unexpected advantage for the claimed process." However, it is respectfully submitted that the instant specification contains adequate disclosure of such "unexpected results," and the claims involve much more than mere mixing of two compounds.

For example, the Examiner is requested to review the Examples 1–5 provided at pages 41–44 of the instant specification, wherein it is expressly stated that a composition comprising the two antibodies (Cetuximab, EMD 72 000) results in increased binding to cell-surface receptors (per cell), enhanced cell aggregation, enhanced inhibition of ligand-binding to cognate EGF receptor(s), enhanced displacement of bound ligands, and increased receptor internalization. See, also the disclosure contained in Figs. 1–5 and the description thereof at page 41 of the specification.

Therefore, it is respectfully submitted that the instantly claimed subject matter is fully inventive over the cited references and that the Office Action has failed to meet the basic criteria for *prima facie* case of obviousness. As such, all the rejections under 35 U.S.C. §103(a) must be withdrawn.

Greene, Bendig et al (US 5,558,864) in combination with Ye et al (*Oncogene*, 1999)

The Office Action at page 13 alleges that "it would have been prima facie obvious to substitute the murine or chimeric 425 antibody that binds to an ErbB1 receptor (as taught by Greene) for the humanized version of Mab425 (as taught by Bendig) and combine with c225 antibody (as taught by Ye) to form a pharmaceutical comprising humanized Mab225 (hMab225) and chimeric Mab225 (c225)." Applicants respectfully traverse this contention.

The inability of the primary Greene reference to meet all the structural and/or functional elements of the antibody molecules recited in Applicants' claims have been discussed *supra*. Greene's emphasis on a structurally distinct receptor molecule (ErbB2) moreover leads a skilled worker away from the subject matter of the present claims. The cited Bendig and Ye secondary references are generically drawn to humanized MAb425 (hMAb425) and chimeric MAb225 (cMAb225), respectively. Again, the Office Action is merely alleging one could arrive at this from the prior art. But this is insufficient. It is required that the PTO establish that one of ordinary skill would arrive at the claimed invention from the references. Therefore, it is respectfully submitted that the Office Action has failed to meet the basic criteria for *prima facie* case of obviousness, and as such, the rejection under 35 U.S.C. §103(a) must be withdrawn.

Claims directed to the pharmaceutical composition in combination with cytotoxic agents

In the paragraphs bridging pages 13–18, the Office Action relies on various references to contend that the claims drawn to the pharmaceutical composition in combination with various cytotoxic agents are rendered obvious by the disclosure contained in the aforementioned primary/secondary references, in view of the tertiary references. This contention is respectfully traversed.

The various limitations of the cited Greene, Mendelsohn, Bendig, and/or Ye references have been discussed *supra*. The Examiner is courteously requested to take note of the limitations of the cited primary and/or secondary references. For example, insofar as none of the primary references teaches a composition which meets the recited structural and functional properties of the antibody molecules which constitute the claimed compositions, the compositions, and methods of using such are both novel and unobvious over the cited primary and/or secondary references.

The additionally cited references generically describe the use of cytotoxic agents in tumor therapy. There is no teaching or suggestion in these references to utilize a composition that meets the structural and functional aspects recited in Applicants' claims. As explicitly stated in §2143 of the MPEP, to establish prima facie case of obviousness, the prior art reference (or references when combined) must teach or suggest all the claim limitations. Such has not been established. Withdrawal of the rejection is courteously requested.

Rejection under 35 U.S.C. § 112, ¶1 (written description)

In the paragraph bridging pages 7 and 8 of the Office Action, it is alleged that "Applicants' specification discloses only a pharmaceutical composition a combination of two antibodies or a binding fragment thereof that binds to different epitopes on the extracellular domain of ErbB1 receptor to which the ligand binds." Insofar as the current claims conform to what the Office Action concedes as being supported by adequate written description, any contention on lack thereof is rendered moot. Applicants' amendment of the claims is not to be construed as acquiesce to this or any other ground of rejection.

With respect to fusion proteins comprising cytotoxic agents, Applicants respectfully submit that techniques for producing and testing such fusion proteins were known in the art well-before the filing date of the instant application. See, the disclosure contained in the paragraphs bridging page 25, line 4 to page 26, line 8 of the instant specification. A simple search on PUBMED with the terms "fusion protein" and "monoclonal antibody" before the earliest priority date revealed more than 100 publications containing such terms. See, for example, Exhibit A.

The specification need not disclose, and preferably omits, what is well known to those skilled in the art. See, e.g., *In re Buchner*, 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991); *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986), cert. denied, 480 U.S. 947 (1987). See, also, MPEP §2164.05(a). Indeed, the Federal Circuit found that an application, which failed to disclose the amino acid sequence of a claimed protein, was not deficient in the written description requirement, despite the fact that the undisclosed sequence was an essential part of the protein's description. See, *Capon v. Eshhar v. Dudas*, (Fed. Cir. 2005) 418 F.3d 1349, 76 U.S.P.Q.2d 1078. Likewise, in the instant application, the

specification need not provide expressed guidance on the structural features of the claimed antibodies, as such were not only known, but also commercially available to a skilled worker before the application was filed. However, in order to facilitate prosecution, representative examples of such fusion proteins are now presented in claim 38. Withdrawal of the rejection is respectfully requested.

In light of these arguments and remarks, it is respectfully submitted that Applicants' disclosure more than reasonably conveys to one of ordinary skill in the art that, as of the filing date, Applicants' had possession of the claimed subject matter.

Rejection under 35 U.S.C. § 112, ¶1 (enablement)

Pages 4–7 of the Office Action alleges that the specification does not enable pharmaceutical composition comprising an antibody other than the antibodies having the capability to bind to different epitopes located in the same ErbB1 receptor molecule. See page 5, last paragraph. In pages 6 and 7, the Office Action relies on Gura et al., Dempsey et al., and McInnes et al. to content that the method of treatment claims are non-enabled. Applicants respectfully traverse these contentions.

At the outset, Applicants courteously submit that a copy of the cited publication by Stryer has not been made available, nor was a citation to the reference provided in the Office Action. Thus, the lack-of-enablement rejection based on this reference should be held in abeyance until the reference is furnished by the PTO. Moreover, Applicants submit that since as the PTO's reliance on the Dermer, Gura, and/or McInnes references is misplaced, the entirety of the lack-of-enablement rejection should be withdrawn.

Dermer et al. (*Bio/Technology*, 1994) cannot be used to evaluate the "state of the art" as the publication is fully ten years before the filing date of the instant application. Given the rapid technological progress made in the post-genomic era, a skilled artisan would instantly question the applicability of such disclosure toward providing a fair and reliable appraisal of the state of the art concerning Applicants' instant invention. One skilled in the art would not be persuaded by such outdated publications to doubt the veracity of statements in Applicants' specification and/or the references cited therein.

Gura and McInnes (both published in 1997) discuss receptor heterogeneity in the ErbB1 receptor family. However, both publications are dated at least seven years before the filing date of the instant Application. In light of the PTO's misplaced reliance

on Dermer and Gura, the ensuing lack-of-enablement rejection should be duly withdrawn in view of the fact that Applicants' specification, coupled with a skilled worker's knowledge (as evidenced by the above-cited Greene, Bendig, Mendelsohn, and Ye publications), provides more than adequate guidance on how to make the claimed compounds and use them for the purposes claimed herein. The specification provides both general and specific guidance regarding the relationship between antibody-mediated receptor inactivation and its actions *in vivo*. See, for example, the disclosure contained in the paragraphs bridging pages 4 and 5 of the instant specification.

The burden is upon the Patent and Trademark Office to provide evidence shedding doubt that the invention can not be made and used as stated; see for example, *In re Marzocchi*, 439, F. 2d 220, 169 USPQ 367 (CCPA 1971). Moreover, decades of scientific studies, both at the basic and clinical levels, have established that *in vitro* studies "reasonably correlate" with their *in vivo* counterparts. In this regard, the Examiner is cordially invited to review the attached copy of *Fiebig et al.*, European Journal of Cancer, 40 (2004) 802-820, showing correlation of *in vitro* activity to *in vivo* activity as the basis for anticancer drug discovery. There is no basis for the general allegation that "clinical correlations are generally lacking" for *in vitro* assays and/or cell-culture based assays.

Alleged lack of in vivo data and other clinical data

The Office Action at page 7 alleges that "a composition for treating cancer without in vivo working example is unpredictable." This contention is without legal basis.

Furthermore, the patent law is in accord with the realities of pharmaceutical arts.

In *Cross v. Iizuka*, 224 USPQ 739 (Fed. Cir. 1985), discussed *supra* the court affirming the decision on reliance on *in vitro* data, and the decision stated that

> *in vitro* results with respect to the particular pharmacological activity are generally predictive of *in vivo* test results, i.e., there is a reasonable correlation therebetween. Were this not so, the testing procedures of the pharmaceutical industry would not be as they are.

The court in *Cross* decision also noted the following

> Knowledge of the pharmacological activities of compounds is

> beneficial to the medical profession, and requiring Iizuka to have disclosed in vivo dosages in the Japanese priority application would delay and frustrate researchers by failing to provide an incentive for early public disclosure of such compounds, thereby failing to further the public interest.
> ...
> Successful in vitro testing will marshal resources and direct the expenditure of effort to further in vivo testing of the most potent compounds, thereby providing an immediate benefit to the public, analogous to the benefit provided by the showing of an in vivo utility.

The Federal Circuit in *Fujikawa v. Watanasin*, 39 USPQ.2d 1895 (1996), stated that

> all that is required is the test to be reasonably indicative of the desired pharmacological response. ... There must be a sufficient correlation between the tests and the asserted pharmacological activity so as to convince those skilled in the art, to a reasonable probability, that the novel compound will exhibit the asserted pharmacological behavior.

Also, the court in *Brana 51 F.3d 1560,* 34 USPQ2d 1436 (Fed. Cir. 1995) stated that

> it is our firm conviction that one who has taught the public that a compound exhibits some desirable pharmaceutical property in a standard experimental animal has made a significant and useful contribution to the art, even though it may eventually appear that the compound is without value in the treatment of humans.

Applicants also point to *In re Bundy*, 642 F.2d 430, 209 USPQ 48, (CCPA 1981), where the disclosure established the basic pharmacology for the compounds, but where no examples were provided. The *Bundy* specification stated that the compounds of the invention possessed activity similar to E-type prostaglandins. Nevertheless it was found that sufficient guidance as to use were given in the disclosure. The court held that "what is necessary to satisfy the how-to-use requirement of §112 is the disclosure of some activity coupled with knowledge as to the use of this activity."

Thus, neither the reality of the pharmaceutical arts or industry or the state of the law in this area provide basis for the broad allegations on pages 6 and 7 of the Office Action. Thus, the rejection is without merit and should be withdrawn.

As such, it is respectfully submitted that within the current state of the art at the time of filing there is no basis for a rejection for lack of enablement in a case where Applicants provide more than sufficient guidance as to how the molecules can be made and their activity tested. Favorable reconsideration is respectfully requested.

In view of the above remarks, favorable reconsideration is courteously requested. If there are any remaining issues which could be expedited by a telephone conference, the Examiner is courteously invited to telephone counsel at the number indicated below.

The Commissioner is hereby authorized to charge any fees associated with this response to Deposit Account No. 13-3402.

Respectfully submitted,

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Attorney Docket No.: MERCK-2990

Date: December 3, 2007